II. REMARKS/ARGUMENTS

A. Status of Claims

Claims 38, 47, 49-53, 56, 60, and 62-73 have been amended without prejudice or admission.

Applicants respectfully submit that no new matter has been added by virtue of the present amendments.

Claims 38 and 47-73 are pending.

Applicants submit that the elected invention and the elected species are encompassed by claims 38 and 47-73.

B. Information Disclosure Statement

The Office Action indicates that the Information Disclosure Statement filed on April 5, 2010, submitting copies of the Office Actions issued in connection with U.S. Serial Nos. 09/154,354; 10/033,055; 10/056,647; 10/056,475; 10/057,630; 10/057,631; 10/057,632; 11/698,394; and 11/829,938, "has been placed in the application file, but the information referred to therein has not been considered," apparently because the Office Actions were not listed on Form PTO-1449.

In response, Applicants respectfully submit that an Information Disclosure Statement re-submitting copies of the Office Actions from these applications and listing each Office Action on Form PTO-1449 is being filed concurrently herewith.

Applicants respectfully request that the information in the Office Actions be considered and made of record in the present application.

C. 35 U.S.C. §103 Rejection over U.S. Patent No. 4,569,937 to Baker et al.; Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S)

Claims 38, 47, 48, 50-52, 62, 63, 66 and 68-69 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 4,569,937 to Baker et al. ("the Baker patent"), Friedel et al. (Drugs, 1993. Vol. 45(1), pp. 131-156) ("Friedel article"); and Eversmeyer et al. (American Journal of Medicine, Aug. 1993, Vol. 95, pp. 10S-18S) ("Eversmeyer article"). According to page 8 of the Office Action, the Friedel and Eversmeyer articles are cited "to teach the pharmacokinetic properties of Nabumetone and demonstrate that nabumetone and ibuprofen are functional equivalents." Office Action, page 10. The Examiner takes a position that "as ibuprofen and nabumetone are functional equivalents (both function as NSAIDs) ... it would be obvious to one of skill in the art to substitute one for the other, with reasonable expectation of success, absent evidence to the contrary." Id.

The rejection is traversed, for the reasons presented in the response filed on March 24, 2010, which is hereby incorporated by reference, as supplemented by the reasons given below.

According to the Manual of Patent Examining Procedure, "[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on ... the mere fact that the components at issue are functional ... equivalents." MPEP, section 2144.06 (emphasis added).

In the present case, the cited references do not recognize equivalency of ibuprofen and nabumetone, as there is nothing in the cited references that suggests that nabumetone-oxycodone combination may exhibit "unexpectedly enhanced analgesic activity" of the ibuprofen-oxycodone combination described in the Baker patent or may be synergistically effective as described in the Baker patent. The Baker patent states that its ibuprofen combination comprises "**synergistically** effective analgesic amounts of

oxycodone ... and ibuprofen ...." Column 2, lines 19-24 (emphasis added). The "unexpectedly enhanced analgesic activity of" the ibuprofen-oxycodone combination was established by an application "of an equieffective dose substitution model and a curvilinear regression analysis utilizing all the data for the individual compounds and various dose ratios for the combinations." Column 3, lines 19-26. In fact, the Examiner appears to acknowledge the synergistic nature of the Baker patent's ibuprofen-oxycodone combination, e.g., on page 5 of the Office Action ("... Baker would teach the use of therapeutic and sub-therapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combination ...").

Applicants submit that there is nothing in the Baker patent that suggests any synergy between nabumetone and oxycodone. In fact, the Baker patent does not even mention nabumetone. There is also nothing in the Friedel and Eversmeyer articles that suggests any synergy between nabumetone and oxycodone. In fact, these articles do not even describe any nabumetone-oxycodone combinations or administrations of nabumetone-oxycodone combinations. The cited references therefore do not recognize and cannot establish the purported equivalency of ibuprofen and nabumetone in the compositions of Baker (i.e., in combination with oxycodone).

Applicants further submit that nabumetone and ibuprofen are not functional equivalents, at the very least because they do not have the same selectivity for COX-1 and COX-2 enzymes.

For these reasons, Applicants submit that the equivalency rationale cannot be used to support the present rejection. See, e.g., MPEP, section 2144.06 ("[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on ... the mere fact that the components at issue are functional ... equivalents").

Applicants further submit that the combination of the cited references does not provide any motivation or suggestion for the skilled person to modify the compositions of the Baker patent by replacing ibuprofen with nabumetone.

The Examiner takes a position on page 6 of the Office Action that "one of ordinary skill in the art would have been motivated to substitute nabumetone and/or pharmaceutically acceptable salt thereof (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g., as compared to ibuprofen)."

The Eversmeyer article however states that a percentage of patients experiencing "at least one adverse effect that was considered by the investigator to be related or probably related to therapy" was **higher** in patients treated with nabumetone than in patients treated with ibuprofen (33.3% of patients treated with nabumetone experienced at least one adverse effect related or probably related to therapy, as compared to 25.5% of patients treated with ibuprofen). See the Eversmeyer article, page 2A-12S. In other words, according to the Eversmeyer article, a patient treated with nabumetone was more likely to experience at least one side effect related or probably related to therapy, as compared to a patient treated with ibuprofen.

Further, according to the Eversmeyer and Friedel articles, the incidence of gastrointestinal side effects were not lower in patients treated with nabumetone than in patients treated with ibuprofen. The Friedel article states that in comparative studies in which statistical analyses were performed, "the incidence of gastrointestinal symptoms attributed to nabumetone was comparable with that of ... ibuprofen ...." See the Friedel article, page 150, right column. Similarly, the Eversmeyer article states that "there was no statistically significant difference among treatment groups because both nabumetone and ibuprofen caused only modest increase in the degree of GI distress," and that "the percent change from baseline in GI distress was 14% with both nabumetone and ibuprofen." See the Eversmeyer article, page 2A-15S, right column. The Eversmeyer

article further states that "significantly more nabumetone-treated patient reported diarrhea than did patients treated with ... ibuprofen ...." Id. at 2A-17S. Specifically, according to the Eversmeyer article, diarrhea "occurred **in more** ($p<0.003$) patients treated with nabumetone (7%) than in patient treated with ... ibuprofen (0.9%) ...." The Eversmeyer article, pages 2A-12S to 2A-13S.

With respect to the physician assessed degree of recovery, the Friedel article states that "ibuprofen was **superior** to nabumetone in the physician assessed degree of recovery." See the Friedel article, page 147, left column (emphasis added).

For the foregoing reasons, Applicants submit that the combination of the cited references would not have provided any motivation or suggestion for the skilled person to modify the compositions of the Baker patent by replacing ibuprofen with nabumetone. This is especially clear in view of the fact that the cited references do not teach or suggest that gastrointestinal side effects are a concern with the compositions described in the Baker patent, or that a combination of nabumetone and oxycodone may be synergistic as described in the Baker patent.

Applicants respectfully reiterate that the combination of the cited references does not teach or suggest administering nabumetone together with oxycodone, e.g., because the Friedel and Eversmeyer articles (which were relied upon by the Examiner for the teaching of nabumetone) describe administration of nabumetone by itself, without any additional analgesic agents, and the Baker patent does not mention nabumetone. As explained above, ibuprofen and nabumetone are not functional equivalents, and the cited references do not recognize their equivalency.

With further regard to claim 50, Applicants submit that the combination of the cited references does not provide any reason for combining nabumetone with a pharmaceutically acceptable excipient "which provides a sustained release of nabumetone" as recited in claim 50, e.g., because the Friedel article describes a mean elimination half-life of, e.g., 38.8 and 26.3 hours, after administration of a single dose of

1 g of nabumetone. See the Friedel article, page 141. The disclosure of elimination half-life of 38.8 and 26.3 hours of nabumetone is significant because it would appear to demonstrate that it is not necessary to combine nabumetone with a sustained release material to produce a prolonged effect of nabumetone. Contrary to the Examiner's assertion, the Baker patent cannot satisfy this limitation, because, as acknowledged by the Examiner, the Baker patent does not teach nabumetone.

With further regard to claim 62 and in response to the Examiner's statement on page 4 of the Office Action that "Baker also inherently teaches inclusion of oxycodone and at least one salt thereof as recited in claim 62, because it is an inherent property of the oxycodone salt (such as oxycodone HCl) to comprise the Oxycodone compound itself," Applicants respectfully submit that "oxycodone" in present claim 62 refers to oxycodone free base, rather than the oxycodone component of the oxycodone salt.

With further regard to claims 68 and 69, Applicants submit that the combination of the cited references does not teach or suggest administering "from 25 mg to 300 mg of nabumetone" or "100 mg of nabumetone" as recited in these claims, respectively, e.g., because the Friedel and Eversmeyer articles describe administration of much higher doses of nabumetone (e.g., 500 mg to 2000 mg). With respect to the Examiner's reliance on the daily dosage of "10 mg to 120 mg/kg" and "60 to 300 mg" of the Baker patent, Applicants point out that the amounts relied upon by the Examiner are for ibuprofen, rather than nabumetone. Ibuprofen and nabumetone are different compounds, which, according to the cited references are administered in different amounts.

With respect to the secondary considerations of non-obviousness, Applicants respectfully note that based on their believe, there is no approved product comprising oxycodone and nabumetone currently on the market, more than 26 years after the filing date of the Baker patent, which further supports Applicants' position that it was not obvious to the skilled person to modify compositions of Baker by replacing ibuprofen with nabumetone.

In response to the Examiner's reliance on In re Kerkhoven on pages 7 and 16 of the Office Action, Applicants respectfully submit that the facts of In re Kerkhoven are not sufficiently similar to the present case, and thus In re Kerkhoven should not be used to support the present rejection. See, e.g., MPEP 2144.04. For example, the present invention involves the destruction of the compositions described in the primary reference by substituting one element of the composition for another, rather than merely combine two compositions to form a third composition.

For the foregoing reasons, reconsideration and withdrawal of the rejection is respectfully requested.

D. 35 U.S.C. § 103 (a) Rejection over Baker et al., Friedel et al. and Eversmeyer et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

Claims 38, 47-67 and 70-73 were rejected under 35 U.S.C. § 103(a) over the Baker patent, Friedel article, Eversmeyer article, and Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195).

The rejection is traversed for the reasons presented in the response filed on March 24, 2010, which is hereby incorporated by reference, as supplemented by the reasons given below.

Applicants respectfully submit that, for the reasons given above, the combination of the cited references does not recognize equivalency of ibuprofen and nabumetone, and that the equivalency rationale cannot be used to support the present rejection. See, e.g., MPEP, section 2144.06 ("[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art…").

Applicants further submit that the combination of the cited references does not provide motivation or suggestion for the skilled person to modify the compositions of the Baker patent by replacing ibuprofen with nabumetone, for the reasons given above.

Applicants respectfully reiterate that the combination of the cited references does not teach or suggest administration of nabumetone in combination with oxycodone as recited in claims 38, 53, 62, and 68-73, or nabumetone in an immediate release form coated over the oxycodone which is in the sustained release form as recited in claim 53.

Reconsideration and withdrawal of the rejection is respectfully requested.

E. Rejection under 35 U.S.C. § 103(a) over U.S. Patent No. 5,840,731 to Mayer et al.

Claims 38, 47-52 and 62-66 were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,840,731 to Mayer et al. (the "Mayer patent"), and if necessary in view of the Friedel and Eversmeyer articles.

The rejection is traversed, for the reasons presented in the response filed on March 24, 2010, which is hereby incorporated by reference, as supplemented by the reasons given below.

In an effort to advance prosecution and further differentiate over the cited references, independent claims 38 and 62 have been amended to recite that the claimed methods "consist[] of orally administering to a human patient an oral dosage form consisting essentially of (i) nabumetone and[/or] at least one pharmaceutically acceptable salt thereof; (ii) oxycodone and[/or] at least one pharmaceutically acceptable salt thereof; and (iii) at least one pharmaceutically acceptable excipient."

Applicants respectfully submit that these amendments exclude the possibility of an analgesic enhancer of the Mayer patent (i.e., "a nontoxic NMDA receptor blocker and/or a nontoxic substance that blocks at least one major intracellular consequence of NMDA receptor activation") from being utilized in methods of present claims 38 or 62 or present in the dosage forms of claims 38 or 52. The phrase "consisting essentially of"

precludes the presence of an active agent other than nabumetone and oxycodone (i.e., excludes the analgesic enhancer of the Mayer patent) in the dosage forms recited in claims 38 and 62, because the present specification makes it clear, e.g., on page 1, lines 7-10, that the present invention "relates to analgesic pharmaceutical compositions containing an opioid analgesic and a cylooxygenase-2 (COX-2) inhibitor" and "methods of treating pain comprising administering such pharmaceutical compositions to humans;" and does not mention an analgesia enhancer such as described in the Mayer patent.

Applicants respectfully submit that a dosage form in accordance with the Mayer patent (alone or in combination with the Friedel and Eversmeyer articles) would necessarily include the analgesic enhancer of the Mayer patent.

The Examiner takes the position on page 18 of the Office Action that the analgesic enhancer of the Mayer patent is "an optional ingredient and can be excluded." Office Action, page 18.

Applicants respectfully disagree with the Examiner's position. The Mayer patent states that in accordance with Mayer's invention "there is provided a method of alleviating pain which comprises administering to a mammal exhibiting pain (a) an analgesia-inducing amount of an NSAID and (b) **an analgesia enhancing amount of at least one analgesia enhancer** selected from the group consisting of nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation with (a) being administered prior to, with, or following administration of (b)" (emphasis added). Column 2, lines 21-32. Further, each exemplified composition of the Mayer patent includes dextromethorphan HBr, an analgesic enhancer of the Mayer patent. See, column 7, lines 15-63. Moreover, the only independent claim of the Mayer patent recites that the claimed method includes administration of the analgesic enhancer of the Mayer patent (i.e., dextromethorphan, dextrorphane or a pharmaceutically acceptable salt thereof.). Accordingly, the analgesic enhancer is a mandatory ingredient in the teaching of the Mayer patent, rather than "an optional ingredient" as asserted by the Examiner.

The lists of analgesic enhancers in columns 3-5 of the Mayer patent do not include oxycodone and nabumetone recited in the present claims. Further, oxycodone is believed to exhibit its analgesic effects through activation of μ and κ opioid receptors, and nabumetone is believed to exhibit its analgesic effect through inhibition of COX enzymes. There is nothing in the cited references that suggests that the combination of oxycodone and nabumetone may have any effect on the NMDA receptor or blocks at least one major intracellular consequence of NMDA receptor activation as described in the Mayer patent. The analgesic enhancer of the Mayer patent is therefore clearly excluded from the scope of claims 38 and 62 as amended herein.

With further regard to claims 68, 69, 72 and 73, Applicants respectfully submit that for the reasons given above, the combination of the cited references does not teach or suggest administering "from 25 mg to 300 mg of nabumetone" or "100 mg of nabumetone" as recited in these claims, e.g., because the Friedel and Eversmeyer articles describe administration of much higher doses of nabumetone (e.g., 500 mg to 2000 mg of nabumetone).

For the foregoing reasons, Applicants submit that the combination of the cited references does not render independent claims 38 and 62 or their dependent claims obvious.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview would advance the prosecution of the application.

Respectfully submitted,
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